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Preparation of Di-*tert*-Butyl [U-^{15}N]-Azodicarboxylate and [U-^{15}N]-(S)-Piperazic Acid

John M. Herbert

Isotope Chemistry Laboratories, Department of Preclinical Metabolism and Pharmacokinetics, Sanofi Research, Willowburn Ave., Alnwick, Northumberland NE66 2JH, UK

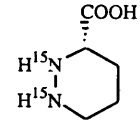
SUMMARY

A convenient one-pot bis-protection of [U-^{15}N]-hydrazine using Boc-ON is described, the product being oxidised efficiently to di-*tert*-butyl [U-^{15}N]-azodicarboxylate which is converted into [U-^{15}N]-(S)-piperazic acid using known methodology.

Key Words: Nitrogen-15; Di-*tert*-butyl [U-^{15}N]-Azodicarboxylate; [U-^{15}N]-(S)-Piperazic Acid.

INTRODUCTION

Piperazic acid is a key intermediate in syntheses of various phamacologically active molecules.[1-3] As part of a discovery programme it was planned to investigate the bound conformations of a class of conformationally-restricted ligands[4] of Interleukin Converting Enzyme, based on this subunit, by ^{15}N NMR. A source of [U-^{15}N]-(S)-piperazic acid (**1**) was therefore required.



1 (**1a**; .CF_3COOH)

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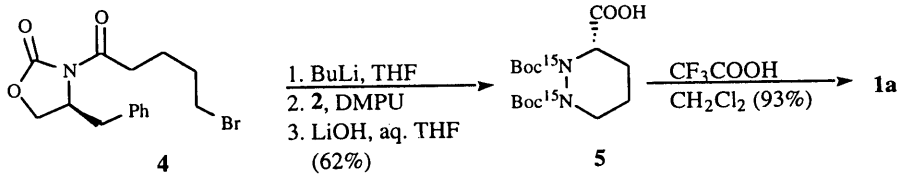
RESULTS AND DISCUSSION

The simplest reported method for assembly of **1** involves stepwise Michael addition and ring closure of di-*tert*-butyl azodicarboxylate (**2**) with an Evans-type homochiral amide of 5-bromovaleric acid.[2] The key requirement is therefore for an efficient preparation of **2**. Although the formation of **2** by NBS oxidation of di-*tert*-butyl hydrazodicarboxylate is a simple process,[5] the formation of the latter from hydrazine has always required a two-step protection process, and the introduction of the second *tert*-butyloxycarbonyl group requires hazardous reagents.[6]

$$H_2{}^{15}N{}^{15}NH_2.H_2SO_4 \xrightarrow[(88\%)]{\text{Boc-ON}} \underset{\mathbf{3}}{BocH^{15}N^{15}NHBoc} \xrightarrow[(98\%)]{\text{NBS}} \underset{\mathbf{2}}{Boc^{15}N{=}{}^{15}NBoc}$$

Scheme 1. Formation of **2** from [U-^{15}N]-Hydrazine Sulfate

Treatment with an excess of Boc-ON provided a direct preparation of **3** from [U-^{15}N]-hydrazine sulfate in a good yield. Purification of this intermediate was relatively straightforward, as was its oxidation[5] to **2** (Scheme 1). Subsequent transformation to **5** was conveniently carried out without purification of the intermediate stages. Hence, treatment of **2** with the anion derived from homochiral amide **4**, and hydrolysis of the product, gave the acid **5** which was converted directly to the trifluoroacetate salt, **1a**.[2] It was not necessary to purify any intermediates and this is therefore a convenient and direct preparation of **1**. The specific rotation of **1a** was marginally higher than that quoted for unlabelled material, consistent with an essentially enantiomerically pure product.



Scheme 2. Cycloaddition of **2** with **4** and elaboration to **1a**.

EXPERIMENTAL

Elemental analyses were carried out by C.H.N. Analysis ltd. (Leicester, U.K.). Optical rotation was measured using an Optical Activity polarimeter, n.m.r. spectra were recorded using a Jeol GSX-270

instrument, and mass spectra were recorded using a VG Autospec magnetic sector instrument at the University of York. Reagents were obtained commercially, [U-^{15}N]-hydrazine sulfate in particular being obtained from Isotec Inc.

Di-*tert*-butyl [U-^{15}N]-Hydrazodicarboxylate (3). Triethylamine (8.9 ml) was added to a stirred suspension of [U-^{15}N]-hydrazine sulfate (2.068 g, 16 mmol) and 2-(*tert*-butyloxycarbonyloximino)-2-phenylacetonitrile (Boc-ON; 7.88 g, 32 mmol) in water/THF (16 ml:20 ml) at room temperature, and the resulting yellow solution was stirred for 24 h. The mixture was partitioned between ethyl acetate and 4N aqueous sodium hydroxide, and the organic phase dried ($MgSO_4$) and concentrated under reduced pressure to give a white solid which was purified by filtration through silica gel in 1:2 ethyl acetate - hexane to give di-*tert*-butyl [U-^{15}N]-hydrazodicarboxylate (**3**; 3.252 g, 88%) as a white solid, m.p.119-119.5°C. $\delta_H(CDCl_3)$ 1.42 (s); *m/z* (CI$^+$) 252 ([MNH_4]$^+$), 235 ([MH]$^+$), 135 (100%, Boc^{15}NH^{15}NH$_3^+$); HRMS found: 252.1706 (calc. for $C_{10}H_{24}N^{15}N_2O_4$ 252.1707).

Di-*tert*-butyl [U-^{15}N]-Azodicarboxylate (2). N-Bromosuccinimide (2.50 g, 13.9 mmol) was added to a stirred solution of **3** (3.25 g, 13.9 mmol) in dichloromethane (30 ml) containing pyridine (1.12 ml, 13.9 mmol). After 5 min, the mixture was washed twice with water and once with 1N aqueous sodium hydroxide, dried ($MgSO_4$) and concentrated under reduced pressure to give **2** (3.151 g, 98%) as a yellow solid, m.p. 84-85°C. $\delta_H(CDCl_3)$ 1.62; *m/z* 250 ([MNH_4]$^+$), 135 (100%); HRMS found: 250.1548 (calc. for $C_{10}H_{22}N_{15}N_2O_4$ 250.1551).

(S)-[U-^{15}N]-Piperazic Acid Trifluoroacetate (1a). To LDA, generated from butyllithium (14.6 mmol) and diisopropylamine (14.6 mmol) in THF (12 ml) under nitrogen at -78°C, a cooled (-78°C) solution of **4** (5.0 g, 14.6 mmol) in THF (15 ml) was added, followed after 30 minutes by a solution of **2** (3.412 g, 14.6 mmol) in dichloromethane (14 ml). The mixture was stirred at -78°C for 30 min, DMPU (40 ml) was added, and the mixture warmed to 0°C, then stirred for a further 90 min. The mixture was partitioned between *tert*-butyl methyl ether and aqueous sodium dihydrogenphosphate, and the organic phase was dried and concentrated to give an oil (6.648 g). This was redissolved in THF (52 ml) and a solution of lithium hydroxide (1.25 g) in water (26 ml) was added with stirring. After 1h, the mixture was washed with *tert*-butyl methyl ether, acidified to pH 2 with 1N hydrochloric acid, and extracted three times with ethyl acetate. The extracts were dried and concentrated under reduced pressure to give **5** (3.014 g, 62%) as an oil. A solution of **5** in

dichloromethane containing trifluoroacetic acid (21 ml) was stirred for 1h, then concentrated and the residue dried by azeotropic distillation with *iso*-propanol, leaving **1a** (2.079 g, 93%) as a white solid, which was recrystallised from *iso*-propanol. m.p. 159-160 °C (lit.[2] 147-149°C). α_D^{19} +12.6° (c 1.0, MeOH; lit.[2] -12.0° for (R) enantiomer). Found: C 34.16, H 4.50, N 11.38, F 23.15; calc. for $C_7H_{11}F_3{}^{15}N_2O_4$: C 34.20, H 4.49, N 11.52, F 22.97 %. $\delta_H(CD_3SOCD_3)$ 1.5-1.85 (3H, m), 1.99 (1H, m), 2.94 (1H, m), 3.11 (1H, m), 3.71 (1H, dd); $\delta_N(CD_3SOCD_3)$ -296.0, -309.7; *m/z* 132 ($M^{+\cdot}$), 87 (100%); HRMS found: 132.0686 (calc. for $C_5H_{10}{}^{15}N_2O_2$ 132.0683).

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